41. (Amended) The composition of claim 37 wherein the cartilage oligomeric matrix protein is human cartilage oligomeric matrix protein purified in a calcium-replete environment.

REMARKS

Claims 1-7, 12, 13, 17, 19, 37, 39 and 41 have been amended to spell out the terms abbreviated as "COMP" and "hCOMP." Support for these definitions can be found in the Specification, for example at page19, lines 20-21.

Claims 5 and 6 have been amended to use the correct abbreviation for "micromolar."

Claims 12 and 13 have been amended to correct an inadvertent error. Support for this amendment can be found in the Specification, for example at page31, lines 23-27.

No new matter has been added.

Applicants respectfully request clarification of the "Disposition of Claims" recited on the "Office Action Summary" with the Office Action dated 11/20/2001. Applicants believe that the correct classification of the claims as of the 11/20/2001 mailing date of the Office Action is as follows:

Claims 1-89 are pending.

Claims 8-11, 14-16, 18, 20-36 and 43-89 are withdrawn.

Claims 1-7, 12, 13, 17, 19 and 37-42 are rejected.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected all pending claims under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specific Rejection of Claims 1-7, 12, 13, 17, 19 and 37-42

Claims 1-7, 12, 13, 17, 19 and 37-42 have been found to be indefinite by the Examiner for the use of the terms "COMP" and "hCOMP." Accordingly, the claims have been amended to recite "cartilage oligomeric matrix protein" and "human cartilage oligomeric matrix protein" in place of the abbreviated terms.

Specific Rejection of Claims 1-7

Claims 1-7 have been rejected by the Examiner as being indefinite "because they lack essential steps as claimed in the method of preparing purified hCOMP." Specifically, the "omitted steps are: introducing DNA encoding hCOMP into a vector, transforming or transfecting the clone into the cell and the method of purifying hCOMP." The Applicants respectfully disagree. The MPEP 2173.02, provides guidelines for determining compliance with the requirement for definiteness of 35 U.S.C. §112, second paragraph. Patentable subject matter is expected to have "a reasonable degree of particularity and distinctness." MPEP 2173.02 goes on to state "[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

Following these guidelines, it is the position of the Applicants that further defining the method of Claim 1 is unnecessary, particularly in light of the content of the Specification, which specifically provides examples of cloning, expression and purification of hCOMP (see, for example, Example 1), in view of teachings of methods known in the art, and in view of the level of skill in the art.

One of ordinary skill in the art would readily know how to perform the method as recited in Claim 1 using well-established techniques that are standard in the art. No steps have been omitted in reciting "introducing DNA encoding human cartilage oligomeric matrix protein into cells." Steps a) and b) of Claim 1 have been taught in the prior art. See, for example, Hecht, J.T. *et al.*, *Matrix Biology 17*:269-278, 1998 (reference AV), page 271, bottom of second column, to top of page 272. One of ordinary skill in the art would be able to not only repeat the procedure taught in Hecht *et al.*, but would also be able to devise similar procedures with different vectors, different cell types, different culture medium and different culture conditions, resulting in recombinantly expressed human cartilage oligomeric matrix protein, as the procedures for cloning a known gene into an expression vector, introducing the vector into cells,

and culturing the cells such that the gene is expressed, have been carried out with many different genes, and are familiar to those of ordinary skill in the art.

Purification of human cartilage oligomeric matrix protein and structurally related proteins has been reported in the prior art. See, for example, DiCesare, P.E. *et al., Eur. J. Biochem 223*:927-937, 1994 (reference AU). It is recognized in the art that devising an effective protein purification scheme is often an empirical process in its early stages. However, with purification procedures and physical and binding properties of the protein known from the scientific literature, one of ordinary skill in the art could perform methods that would purify human cartilage oligomeric matrix protein. The discovery missing from the prior art was the inclusion of calcium throughout the purification. Further, one of ordinary skill in the art would know that the purification scheme taught in Example 1 is only one of a number of schemes, using different column chromatography materials and different buffers, for example, that would result in purified human cartilage oligomeric matrix protein.

Specific Rejection of Claims 1-7

Claims 1-7, are also rejected by the Examiner as being indefinite because of the use of the phrase "introducing DNA encoding hCOMP into cells," such that "it is unclear which cells are used for transformation." The Applicants disagree. To one of ordinary skill in the art, it will be readily apparent which cells would be suitable for practicing the current invention. Human COMP has already been expressed in a variety of cell systems. For example, in the instant specification human embryonic kidney (HEK293) cells have been employed. See page 30, lines 13-14, and Figure 1. In Hecht *et al.*, (*Matrix Biology* (1998) *17*: 269; reference AV), human cartilage oligomeric matrix protein was expressed using a baculovirus system (see, for example, page 271, column 2). Thus, it is apparent that one of ordinary skill in the art will be able to determine a suitable cell type into which DNA encoding hCOMP may be introduced.

Specific Rejection of Claims 5, 6 and 37-42

Claims 5, 6 and 37-42 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite because of the use of the term "at least."

Claims 5 and 6 refer to a solution "characterized by a calcium concentration of at least 300 μm." The Examiner questions "what is the maximal calcium concentration." It is the Applicants' position that the maximum calcium concentration is not required to render Claims 5 and 6 definite. It can be easily determined by anyone of ordinary skill in the art what calcium concentrations are effective for purification of human cartilage oligomeric matrix protein. Furthermore, the MPEP at section 2173.05(c) provides guidelines for open-ended numerical ranges, which do not state that "at least" terminology is indefinite and do not state that an upper limit must be given. The Applicants maintain that Claims 5 and 6, particularly when read in the light of the Specification and Claims, are indeed definite.

Claim 37, and dependent claims thereon, are also rejected for the use of the term "at least." Again, Applicants submit that Claim 37 is not rendered indefinite for the use of this term. Specifically, Claim 37 recites ". . . wherein the matrix comprises at least one material selected from the group consisting of . . ." and goes on to list a specific group of materials. The Examiner questions "how many biological matrices are in the composition." The term "at least one" is a limitation on the number of material components to be chosen from the list for inclusion in the biological matrix, not a limitation on the number of biological matrices. The Applicants maintain the position that Claim 37, and dependent claims thereon, are not rendered indefinite for the use of the term "at least one."

Specific Rejection of Claims 12 and 13

Claims 12 and 13 are also rejected under 35 U.S.C. §112, second paragraph, as being indefinite for being "unclear how the cleavage products of hCOMP would be different." Claims 12 and 13 have been amended to bring them into agreement with the written description at page 12, line 28 to page 13, line 3, wherein the bands are described as being 50 kDa and 55 kDa (Claim 12) and 62 kDa and 67 kDa (Claim 13). Applicants bring to the Examiner's attention the Specification at page 13, lines 1-3, which teaches that human cartilage oligomeric matrix protein possesses different conformations that correlate with the presence of different calcium concentrations. Also see page 31, line 14 to page 32, line 2 and Figure 3, illustrating that trypsin digestion of human cartilage oligomeric matrix protein can produce differently sized cleavage products that correlate with the specific conformations of human cartilage oligomeric matrix

protein in different calcium concentrations. When read in light of the teachings of the Specification, the claims cannot be viewed as indefinite. The purified human cartilage oligomeric matrix protein of Claims 12 and 13 are different in their conformations, as can be shown experimentally by the results of trypsin cleavage.

Specific Rejection of Claim 39

Claim 39 is also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the use of the term "a differentiation agent." Applicants disagree. Differentiation agents are readily recognized by one of ordinary skill in the art. From the discussion of page 27, lines 1-27 of the Specification, it is readily understood by one of ordinary skill in the art that a differentiation agent is an agent that when added to chondrogenic cells, stimulates differentiation of those cells into cells more like those found in cartilage. The instant Specification teaches a variety of differentiation agents, for example, at page 27, lines 6-8. Together, the teachings in the relevant art and the Specification provide definite meaning to "a differentiation agent."

Reconsideration and withdrawal of all rejections under 35 U.S.C. §112, second paragraph, are respectfully requested.

Claim Rejection Under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 5 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Hecht *et al.* (*Matrix Biology* (1998) *17*: 269-278) taken with Lawler *et al.* (*J. Biol. Chem.* (1983) *258*: 12098-12101).

According to MPEP 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met:

(1) There must be some suggestion or motivation to combine the reference teachings;

(2) There must be a reasonable expection of success; and

(3) The prior references when combined must teach or suggest all the claim limitations.

The references cited by the Examiner fail to meet these criteria. Hecht *et al.* teach the expression of human cartilage oligomeric matrix protein, but specifically disclose that the conditioned medium containing the recombinant protein was "used for this study without additional purification" (page 272, column 1). Hecht *et al.* not only do not teach human cartilage oligomeric matrix protein purification, they also do not teach either the expression or purification of human cartilage oligomeric matrix protein in the presence of calcium. Lawler *et al.* disclose the protein thrombospondin (TSP-1) isolated from platelet cells. They do not disclose cartilage oligomeric matrix protein, nor the purification of cartilage oligomeric matrix protein from cartilage oligomeric matrix protein-expressing cells. Hecht *et al.* do not teach or suggest anything about TSP-1 purification, and Lawler *et al.* do not teach or suggest anything about cartilage oligomeric matrix protein. Thus the first criterion for establishing *prima facie* obviousness is not met.

One of ordinary skill in the art who wanted to produce human cartilage oligomeric matrix protein by recombinant means and then purify the human cartilage oligomeric matrix protein, would logically turn to the previously used, published methods for the successful purification of cartilage oligomeric matrix protein, for example, the method of DiCesare *et al.* (reference AU) or Mörgelin, M. *et al.*, *J. Biol. Chem. 267*: 6137-6147, 1992 (copy enclosed as Exhibit A). Nothing in the cited references Hecht *et al.* or Lawler *et al.*, or in the combination of references, suggests that the known effective methods for purifying cartilage oligomeric matrix protein should be altered for any reason. Certainly, there is no suggestion in the references, taken together, that calcium should be added to the purification procedure for human cartilage oligomeric matrix protein. One of ordinary skill in the art could not arrive at the claimed invention by combining the two cited references, as Lawler *et al.* do not discuss purified human cartilage oligomeric matrix protein or any steps in its purification, and Hecht *et al.* do not discuss TSP-1 or its purification. Nor does either reference suggest that the purification of human cartilage oligomeric matrix protein and TSP-1 should be similar in any way.

Without meeting each and every criteria for establishing a case of obviousness, the cited references do not support the rejection of Claims 1, 2, 4, 5 and 7 under 35 U.S.C. § 103(a). Furthermore, it is improper to use hindsight reasoning to arrive at the present invention. The US

Court of Appeals in ATD Corp. v. Lydall Inc., 48 USPQ2d 1321, 1329 (Fed. Cir. 1998) stated that:

> Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.

Thus, withdrawal of the rejection is respectfully requested.

Claim 37 is also rejected under 35 U.S.C. §103(a) as being unpatentable over Heinegård *et al.* (WO 98/46253) taken with Junginger (U.S. Patent 4,666,702).

Heinegård *et al.* (WO98/46253) teach a pharmaceutical composition comprising cartilage oligomeric matrix protein, for the treatment of arthritis. For oral administration of the composition, tablets "may be coated with a suitable polymer dissolved in a readily volatile organic solvent." See page 14, lines 7-9. Heinegård *et al.* do not teach a biological matrix comprising any of the materials listed in Claim 37.

Junginger (U.S. Patent 4,666,702) teaches tablets comprising an active drug material and a microporous synthetic thermoplastic polymer. Junginger does not teach the use of polymers in a biological matrix, and does not teach anything about cartilage oligomeric matrix protein.

Combining the teachings of Heinegård *et al.* with the teachings of Junginger, one of ordinary skill in the art would think of tablets for oral administration, comprising cartilage oligomeric matrix protein coated with a microporous synthetic thermoplastic polymer. This is not the invention of Claim 37.

As discussed supra, there are three criteria which must be met in order to establish a *prima facie* case of obviousness. Neither Heinegård *et al.* nor Junginger nor the combination of the two references teaches each and every limitation of Claim 37. Neither reference teaches the structural element of a biological matrix. Furthermore, this structural element is not suggested in either cited reference. Heinegård disclose a tablet which ". . . may be coated with a suitable polymer . . ." (page 14, lines 7-8). There is no suggestion of a matrix-like structure. Junginger does not disclose or suggest a biological matrix. Thus, the cited references fail to meet the

necessary criteria that establish a *prima facie* case of obviousness. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned attorney at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Carol A. Egner

Carol A. Egner
Registration No. 38,866
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: April 22, 2002

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) Purified [hCOMP] human cartilage oligomeric matrix protein prepared by the method comprising:

   a) introducing DNA encoding [hCOMP] human cartilage oligomeric matrix protein into cells, thereby producing cells expressing [hCOMP] human cartilage oligomeric matrix protein;

   b) culturing the cells in a culture medium under conditions suitable for expressing the [hCOMP] human cartilage oligomeric matrix protein, thereby producing expressed [hCOMP] human cartilage oligomeric matrix protein; and

   c) purifying the [hCOMP] human cartilage oligomeric matrix protein in the presence of calcium.

2. (Amended) The purified [hCOMP] human cartilage oligomeric matrix protein of claim 1 wherein the [hCOMP] human cartilage oligomeric matrix protein is purified under calcium-replete conditions.

3. (Amended) The purified [hCOMP] human cartilage oligomeric matrix protein of claim 1 wherein the cells in step b) are cultured in a calcium-replete culture medium.

4. (Amended) The purified [hCOMP] human cartilage oligomeric matrix protein of claim 2 wherein the calcium is present at millimolar levels when the [hCOMP] human cartilage oligomeric matrix protein is purified.

5. (Amended) The purified [hCOMP] human cartilage oligomeric matrix protein of claim 1 wherein the [hCOMP] human cartilage oligomeric matrix protein is purified in a solution characterized by a calcium concentration of at least 300 [*u*M] μM.

6. (Amended) The purified [hCOMP] human cartilage oligomeric matrix protein of claim 1 wherein the [hCOMP] human cartilage oligomeric matrix protein is expressed and purified in a solution characterized by a calcium concentration of at least 300 [*u*M] μM.

7. (Amended) The purified [hCOMP] human cartilage oligomeric matrix protein of claim 1 wherein the cells expressing [hCOMP] human cartilage oligomeric matrix protein are produced by introducing into cells DNA encoding full length [hCOMP] human cartilage oligomeric matrix protein.

12. (Amended) Purified [hCOMP] human cartilage oligomeric matrix protein which digests into bands of 50 kDa [or] and 55 kDa when cleaved by trypsin.

13. (Amended) Purified [hCOMP] human cartilage oligomeric matrix protein which digests into bands of 62 kDa [or] and 67 kDa when cleaved by trypsin.

17. (Amended) An ELISA kit comprising the [hCOMP] human cartilage oligomeric matrix protein of claim 1.

19. (Amended) An ELISA kit comprising [hCOMP] the human cartilage oligomeric matrix protein produced by the method of claim 8.

37. (Amended) A composition comprising purified [COMP] cartilage oligomeric matrix protein and a biological matrix, wherein the matrix comprises at least one material selected from the group consisting of: treated cartilage and bone matrices, collagens, hyaluronan, fibrin gels, carbon fibers, porous polylactic acid, type I collagen gel and type II collagen gel and purified [COMP] cartilage oligomeric matrix protein.

39. (Amended) The composition of claim 37 wherein the [COMP] cartilage oligomeric matrix protein is bound to a differentiation agent.

41. (Amended) The composition of claim 37 wherein the [COMP] cartilage oligomeric matrix protein is [hCOMP] human cartilage oligomeric matrix protein purified in a calcium-replete environment.